DETAILED ACTION

Claims 12, 14, 15, 17-35 are pending.

Applicants response filed May 6, 2011 has been received and entered in the application.

Priority

This application claims benefit to provisional application 60/419,439 (dated 10/18/2002) and provisional application 60/440,177 (dated 01/15/2003).

Action Summary

Claim 12 and 14 is rejected under 35 U.S.C. 112, second paragraph is maintained.

Claims 12, 18-22, 24-27 and 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sweatt et al (U.S.Publication 2002/0058699) and Hall-Jackson et al (Paradoxical activation of Raf by a novel Raf inhibitor, Chemistry & Biology, August 1999, 6:559-568) both are of record is maintained.

Claims 15, 17, 23 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sweatt et al (U.S.Publication 2002/0058699) and Hall-Jackson et al (Paradoxical activation of Raf by a novel Raf inhibitor, Chemistry & Biology, August 1999, 6:559-568) as applied to claims 12, 14, 18-22, 24-27 above, and further in view of

Varga (Involvement of Raf-1 in chronic ç-opioid receptor agonist-mediated adenylyl cyclase superactivation, European Journal of Pharmacology 451, 2002, 101-102) all are of record is maintained. Instant claim 14 is now included in the above rejection due to amendment of claim 14.

Response to Arguments

Applicants argue that a prima facie case of obviousness has not been established. This argument has been fully considered but has not been found persuasive. Sweatt teaches that the amount of activated MAPK in a neuron can be reduced by approaches that cause dephosphorylation of upstream kinases in the MAPK cascade. Thus, compounds that activate phosphatases specific for any members of the MAPK cascade upstream of MAPK will reduce the activity of the upstream kinase, ultimately leading to reduced downstream activity of MAPK. Compounds that effect dephosphorylation of other upstream kinases including Ras, Raf1 (also known as c-raf), B-Raf and Rap1 may be used (paragraph 0027). Hall-Jackson teaches that N-[5-(3-Dimethylaminobenzamide)-2-methylphenyl]-4-hydroxybenzamide (herein after, "ZM 336372") is a potent and specific inhibitor of c-Raf that shows a tenfold selectivity over B-Raf (page 565, first paragraph under Discussion). It would have been obvious to one of ordinary skills in the art at the time of the invention was made to employ the specific c-Raf, ZM 336372 to treat epilepsy (seizure disorder) or individuals susceptible to neurodegenerative disease. One would have been motivated to employ ZM 336372 because ZM 336372 is a potent and effective inhibitor of c-raf and B-raf as taught by

Hall-Jackson. Additionally, since everyone is susceptible to neurodegenerative disease, it would have been obvious to administer c-Raf inhibitors to inhibit neuronal cell death. Therefore, the rejection under 35 U.S.C 103(a) is deemed proper.

Applicants are respectively reminded that arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue that the combination of Sweatt and Hall-Jackson fails to disclose a treatment for individuals susceptible to neurodegenerative diseases. This argument has been fully considered but has not been found persuasive. Since **every** subject is susceptible to neurodegenerative disease, then the administration of a c-raf inhibitor would benefit any and all individuals.

Applicants merely state that epilepsy does not directly cause neuronal loss. This argument has been fully considered but has not been found persuasive. As stated in the previous office action dated January 16, 2011, Roux (p75 Neurotrophin Receptor Expression is induced in Apoptotic Neurons after Seizure, Journal of Neuroscinece, August 15, 1999, 19(16); pages 6887-6896) of record expressly teaches in the abstract that **seizures causes neuronal cell loss in both animal model and human epilepsy**. And that determination of the contribution of apoptotic mechanism to seizure-induced neuronal cell death. Therefore, seizures do in fact cause neuronal cell loss as demonstrated by Roux.

Applicants argue that Sweatt fails to relate to a neurodegenerative disease. And that Sweatt does not fall into the instant specifications definition of neurodegenerative disease. This argument has been fully considered and is persuasive. The instant specification discloses that "epilepsy-associated neuronal loss" is a "Neurodegenerative disease or conditions". Sweatt teaches that seizures can occur in a variety of situations including epilepsy, Parkinson's disease (which is a neurodegenerative disease), trauma, drug addition and cerebral palsy (paragraph 0003). Therefore, Sweatt does teach that seizures may occur in patients with neurodegenerative disease (e.g. Parkinson's disease), or trauma. Sweatt teaches that the amount of activated MAPK in a neuron can be reduced by approaches that cause dephosphorylation of upstream kinases in the MAPK cascade. Thus, compounds that activate phosphatases specific for any members of the MAPK cascade upstream of MAPK will reduce the activity of the upstream kinase, ultimately leading to reduced downstream activity of MAPK. Compounds that effect dephosphorylation of other upstream kinases including Ras, Raf1 (also known as c-raf), B-Raf and Rap1 may be used (paragraph 0027). Hall-Jackson teaches that N-[5-(3- Dimethylaminobenzamide)-2-methylphenyl]-4-hydroxybenzamide (herein after, "ZM 336372") is a potent and specific inhibitor of c-Raf that shows a tenfold selectivity over B-Raf (page 565, first paragraph under Discussion). It would have been obvious to one of ordinary skills in the art at the time of the invention was made to employ the specific c-Raf, ZM 336372 to treat epilepsy (seizure disorder) or individuals susceptible to neurodegenerative disease. One would have been motivated to employ ZM 336372 because ZM 336372 is a potent and effective inhibitor

of c-raf and B-raf as taught by Hall-Jackson. Additionally, since everyone is susceptible to neurodegenerative disease, it would have been obvious to administer c-Raf inhibitors to inhibit neuronal cell death. Therefore, the rejection under 35 U.S.C 103(a) is deemed proper.

For the ease of the applicant the previous office action dated January 16, 2011 is reproduced below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 and 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 12 and 14 has omitted steps. The omitted steps are: what "active steps" are involved in "identify a mammal with apoptotic neuronal cell death ". In the present case, the claims recite a method of inhibiting the neurodegeneration process in a patient. Accordingly, the claims appear to include the active step of identify a mammal with apoptotic neuronal cell death; and therefore, attempt to characterize the patient population. However, it is unclear of what active steps are involved in the process since it is was known at the time of the invention that everyone **(emphasis added)** is at risk or suspected of a neurodegenerative disorder as evidenced by Schulte et al. (American Journal of Public Health, Vol. 86, No 9, Sept. 1996, pages 1281-1288). Accordingly, for prior art purposes, the Examiner will interpret

"identify a mammal with apoptotic neuronal cell death" as any individual is suspected of neurodegenerative disorder in view of the Schulte et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12,18-22, 24-27 and 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sweatt et al (U.S.Publication 2002/0058699) and Hall-Jackson et al (Paradoxical activation of Raf by a novel Raf inhibitor, Chemistry & Biology, August 1999, 6:559-568) both are of record.

Sweatt teaches that the amount of activated MAPK in a neuron can be reduced by approaches that cause dephosphorylation of upstream kinases in the MAPK cascade. Thus, compounds that activate phosphatases specific for any members of the MAPK cascade upstream of MAPK will reduce the activity of the upstream kinase, ultimately leading to reduced downstream activity of MAPK. Compounds that effect dephosphorylation of other upstream kinases including Ras, Raf1 (also known as c-raf), B-Raf and Rap1 may be used (paragraph 0027). Sweatt teaches that compounds that inhibit the activity of kinases upstream of MAPK in the MAPK cascade include c-Rafs (paragraph 0032). Sweatt teaches that such compounds (e.g. c-Raf's) may be administered to humans and mammals (paragraph 0036). Sweatt teaches that c-raf may be used in the treatment of seizure disorders (abstract).

Sweatt does not expressly teach the c-Raf of N-[5-(3-Dimethylaminobenzamide)-2-methylphenyl]-4-hydroxybenzamide

Hall-Jackson teaches that N-[5-(3- Dimethylaminobenzamide)-2-methylphenyl]-4-hydroxybenzamide (herein after, "ZM 336372") is a potent and specific inhibitor of c-Raf that shows a tenfold selectivity over B-Raf (page 565, first paragraph under Discussion). Hall-Jackson teaches that cells (in mammals) have a feedback loop by which Raf suppresses its own activation, so that any inhibition of Raf is rapidly counterbalanced by its reactivation. This implies that cells does contain high specific activity c-Raf that is inhibited from activating its downstream substrate MKK1 because of the presence of the inhibitor (page 565, first paragraph under Discussion). Hall-Jackson teaches that ZM 336372 inhibits c-Raf and B-Raf (page 566, table 4 and first paragraph).

It would have been obvious to one of ordinary skills in the art at the time of the invention was made to employ the specific c-Raf, ZM 336372 to treat epilepsy (seizure disorder) or individuals susceptible to neurodegenerative disease. One would have been motivated to employ ZM 336372 because ZM 336372 is a potent and effective inhibitor of c-raf and B-raf as taught by Hall-Jackson.

Examiner further points out that any individual is susceptible to neurodegenerative disease as the individual ages and would benefit by the administration of c-Raf inhibitors.

With regards to the c-raf inhibitor (e.g. ZM 336372) inhibiting neuronal cell death via B-raf regulation, it is a property of the c-Raf that upon administration of a c-Raf to a mammal that inhibition of cell death via B-raf regulation would be obtained. Furthermore, presence of a property not possessed by the prior art is evidence of nonobviousness. *Inre Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound); *Ex parte Thumm*, 132 USPQ 66 (Bd. App. 1961) (Appellant showed that the claimed range of ethylene diamine was effective for the purpose of producing "regenerated cellulose consisting substantially entirely of skin'" whereas the prior art warned "this compound has practically no effect.' "). The submission of evidence that a new product possesses unexpected properties does not necessarily require a conclusion that the claimed invention is nonobvious. *In re Payne*, 606 F.2d 303, 203 USPQ 245 (CCPA 1979). See the discussion of latent properties and additional advantages in MPEP § 2145.

Claims 14-15, 17, 23 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sweatt et al (U.S.Publication 2002/0058699) and Hall-Jackson et al (Paradoxical activation of Raf by a novel Raf inhibitor, Chemistry & Biology, August 1999, 6:559-568) as applied to claims 12, 14, 18-22, 24-27 above, and further in view of Varga (Involvement of Raf-1 in chronic ç-opioid receptor agonist-mediated adenylyl

cyclase superactivation, European Journal of Pharmacology 451, 2002, 101-102) all are of record.

Neither Sweatt nor Hall-Jackson expressly teach {5-iodo-3- [(3, 5-dibromo-4-hydroxyphenyl) methylene]-2-indolinone} (herein after GW 5074).

Varga teaches that GW 5074 is a c-Raf inhibitor.

It would have been obvious to one of ordinary skills in the art to employ the specific c-Raf of GW 5074 for the treatment of individuals susceptible to neurodegenerative diseases. One would be motivated to employ GW 5074 because GW 5074 is a c-Raf inhibitor as taught by Varga and **everyone is susceptible for neurodegenerative disease and would benefit from the administration of GW 5074.** Therefore, the claim limitations as set forth in claims 15, 17 and 23 have been met.

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Claims 12, 14, 15, 17-35 are rejected.

No claims are allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHRIEN CRUZ whose telephone number is (571)270-5238. The examiner can normally be reached on Mon - Thurs 7:00am - 5:00pm with every Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1628

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